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Myeloablative immunosuppressive treatment with autologous haematopoietic stem cell transplantation in a patient with psoriatic arthropathy and monoclonal gammopathy of undetermined significance

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Transplantation of peripheral blood stem cells (PBSCT) is currently explored in patients with refractory autoimmune diseases,[1 2] and results so far show that about two thirds of patients who receive a transplant benefit from this procedure.[3] Transplant related mortality in patients with autoimmune disease is similar to that seen in patients with non-Hodgkin's lymphoma.[4]

CASE REPORT

We report on a 34 year old male patient with a 16 year history of psoriatic arthropathy with mutilating bilateral lesions of the wrists, metacarpal, proximal and distal interphalangeal and metatarsal, and lower extremity interphalangeal joints, who was refractory to treatment with multiple disease modifying, immunosuppressive substances, including gold, methotrexate (MTX), MTX plus sulfasalazine, cyclosporin A (CSA), mycophenolate mofetil (MMF) alone or in combination with CSA, steroids, and a combination of CSA, MTX, and MMF. IgA κ monoclonal gammopathy of unknown significance developed later in the course of the disease without evidence for either multiple myeloma or systemic amyloidosis. Treatment of arthritis with a non-steroidal anti-inflammatory drug (NSAID) was complicated by a duodenal ulcer. There were only modest psoriatic skin lesions affecting the extensor surfaces of both knees and elbows.

PBSCT was considered in this patient, because tumour necrosis factor α antagonists had not yet been licensed for use in psoriatic arthropathy at that time. We were particularly concerned about the presence of the IgA κ paraprotein, so therapeutic strategies to control symptoms of arthritis also aimed at eliminating the potentially hazardous plasma cell clone. Haematopoietic stem cells were mobilised with cyclophosphamide (Cy) 4000 mg/m^2 and granulocyte-colony stimulating factor (G-CSF) 5 μg/kg. Stem cell apheresis was performed following standard procedures, and T cell depletion of the graft was achieved by CD 34+ selection using the CliniMACS device. CD 34+ cells (11.38×10^6 cells/kg) were harvested. Myeloablative immunosuppression consisted of Cy 200 mg/kg (50 mg/kg/day, days −5 to –2), and in vivo T cell depletion was achieved with antithymocyte globulin (ATG) (Fresenius) 80 mg/kg (20 mg/kg/day, days –4 to –1). CD 34+ cells (5.21×10^6 cells/kg) were retransfused on day 0. An acute flare of arthritis occurred while the patient was receiving G-CSF for stem cell mobilisation, and this was symptomatically treated with an NSAID. Pancytopenia after myeloablative treatment was complicated by neutropenic fever (39.1℃) on day 11, subsiding under standard antibiotic treatment. Mucositis and diarrhoea WHO grade I occurred, lasting for 3 days. Within 3 days after the start of high dose Cy the symptoms of arthritis completely disappeared, as did the psoriatic lesions. As granulocytes did not recover by day 15, G-CSF was started, and no new flare of arthritis was observed. Granulocytes were $>10^9$/l by day 19, platelets $>20\times10^9$/l by day 21, and the erythrocyte sedimentation rate and C reactive protein subsequently normalised.

Clinical findings were confirmed by negative bone scintigraphy on day 21. Within 6 months after PBSCT the IgA κ paraprotein disappeared.

However, 16 months after PBSCT, polyarthritis recurred, although without laboratory evidence of systemic inflammation (erythrocyte sedimentation rate and C reactive protein were within normal limits), apparently now following a more benign course. At present, the patient is receiving low dose MTX (10 mg/week) and a COX-2 selective NSAID (celecoxib) and has only mild signs of arthritis of the right wrist. Monoclonal gammopathy has not reappeared.

DISCUSSION

To our knowledge this is the first report of PBSCT in a patient with psoriatic arthropathy. In rheumatoid arthritis, disease activity decreased markedly in 8 of 12 patients, with patients free from disease modifying antirheumatic drug treatment for a period of 130 days during a 7–21 month follow up after PBSCT.[5] Remission of arthritis in patients with rheumatoid arthritis after PBSCT usually lasts for 6–9 months.[5–7] In our patient relapse of arthritis, with a now more benign course, did not occur until 16 months after PBSCT, possibly owing to a more aggressive immunosuppressive regimen, including in

vivo T cell depletion with ATG and graft manipulation. Three patients with remission of psoriasis (without arthropathy) after PBSCT due to a haematological disease relapsed within 6–14 months as described in a previously published report.[8] However, skin involvement was not of major concern in our patient.

We conclude that it may be worth exploring PBSCT further in young patients with mutilating psoriatic arthropathy who are resistant to disease modifying antirheumatic drugs and for whom tumour necrosis factor α antagonist treatment has failed.

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Peripheral blood lymphocyte phenotypes in patients with spondyloarthropathy

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A prevalent hypothesis in the pathogenesis of the spondyloarthropathies (SpA) is that gut lymphocytes primed by antigens in the gut lumen may enter the bloodstream and home in on target tissues—for example, the entheses and synovial membranes, where they may initiate a local immune process responsible for further local inflammation.[1] Selective homing of lymphocytes is a well known process that is made possible, in part, by the lymphocyte phenotype acquired as a response to antigenic stimulation and characterised by a subset of receptors (such as integrins) associated with targeted trafficking.[2] Among integrins, $\alpha_E\beta_7$, is expressed by T lymphocytes in or adjacent to mucosal epithelia, and exhibits features that indicate a possible role in this pathogenic process.[3 4] To our knowledge, there are no data on the markers for activation and adhesion of circulating lymphocytes in the SpA. The main objective of this study was to look for differences in $\alpha_E\beta_7$ (CD103) blood lymphocyte counts between patients with active and those with inactive SpA, using flow cytometry. We also studied markers for other adhesion molecules, lymphocyte subsets, and lymphocyte activation.

PATIENTS, METHODS, AND RESULTS

Twenty patients meeting European Spondylarthropathy Study Group criteria[5] or Amor's criteria[6] for SpA were enrolled in the study, together with control patients followed up for chronic degenerative low back pain. They did not have any other underlying disease and only had a non-steroidal anti-inflammatory drug (NSAID) or acetaminophen as current treatment. All patients and controls gave their written informed consent to participation in the study, which was approved by the local ethics committee. Table 1 shows the main characteristics of the patients. The 20 control patients had a mean (SD) age of 39.8 (9.6) years ($p>0.05$ *v* the SpA group) and six of them were men. Flow cytometry was performed using a Coulter EPICS(r) XL within 24 hours after staining. List mode parameters were analysed and stored on System II software (Beckman-Coulter).

The studied markers (absolute count and/or percentage of positive cells) were compared between the patients with SpA and the controls, and between the patients with SpA with active disease and those with quiescent or controlled disease. Active disease was defined a priori as a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score $>30^7$ with a C reactive protein (CRP) level >15 mg/l (Mann-Whitney test).

The mean (SD) percentage of CD103 lymphocytes did not differ between the patients with SpA (0.9 (0.4)%) and controls (1 (0.6%)), but was significantly lower in the patients with active SpA (0.66 (0.26%)) than in those with inactive SpA (1.2 (0.7)%, $p<0.05$). Except for a small but significant decrease in the percentage of CD49d positive cells in the patients with SpA as compared with the controls, no significant differences between the groups with active and inactive SpA were seen for any of the three other integrin markers (CD11a, CD29, and CD49d). The frequencies of the main CD4 and CD8 T cell subsets and NK cells were not significantly different between the patients with SpA and controls or between the groups with active and inactive SpA. However, there was a trend toward an increase in the CD3+ lymphocyte count in the group with active SpA, which was